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EXAMINER	
LUNDGREN, JEFFREY S	
ART UNIT	**PAPER NUMBER**
1639	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/908,943	YAN ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Lundgren	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *102-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *102-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Change in Examiner

This application has been reassigned to Examiner Jeff Lundgren, AU 1639. Applicants should note the change for their records and for all future correspondence with the Office regarding this application.

Election/Restrictions

In the Office Action mailed on May 3, 2005, Applicants were required to elect three distinct species encompassed by claims 102-131. Specifically, the Examiner required Applicants to elect a species for each of the following groups:

A. the assay milieu – (i) *in vitro* assay; or (ii) *in vivo* assay;

B. a single polypeptide with beta secretase APP activity;

C. a single secretase substrate (*e.g.*, a specific SEQ ID NO comprising SYEV).

In the Reply filed on June 6, 2005, Applicants elected a species for each group with traverse, and presented arguments to each of the Examiner's reasons for the aforementioned species restriction.

Regarding the species restriction requirement drawn to the assay milieu, Applicants arguments have been considered, and are found persuasive. Accordingly, the species requirement is dropped, and examination of the instant application will include the both the *in vitro* and *in vivo* assay methods.

Regarding the species restriction requirement drawn to a single polypeptide with beta secretase APP activity, Applicants arguments have been considered, and are found persuasive. Accordingly, the species requirement is dropped, and examination of the instant application will include the both species of SEQ ID Nos. 2 and 4.

Regarding the species restriction requirement drawn to the single secretase substrate, Applicants arguments have been considered, and are found persuasive. Accordingly, claims to Applicants' elected invention, *i.e.*, assay methods comprising polypeptides having the substrate sequence –SYEV-, will be examined. The linking claims will be examined, and are treated in the manner set forth at page 11 of the Petition Decision mailed on October 27, 2004. Upon the allowance of the linking claims(s), the restriction requirement as to the linked invention shall be

withdrawn and any claims depending from or otherwise including all the limitations of the linking claim(s) will be entitled to examination in the instant application.

Upon review of the claims in light of the elected species, *i.e.*, assay methods comprising polypeptides having the substrate sequence –SYEV-, it appears that Applicants have mistakenly identified fewer claims than actually read on the elected species. Specifically, it appears that the following claims each encompass the elected group and species SYEV: claims 102-131.

All arguments and issues raised by Applicants have been fully considered and addressed, accordingly, the restriction requirement is made *final*.

Outstanding Rejections

A number of rejections were made in the Office Action mailed on December 15, 2003; in response, Applicants provided a full and complete Reply to the Office Action, received on March 19, 2004. Applicants' Reply has been given full consideration.

Rejection under 35 USC § 112, second paragraph

Claims 21 and 89 have been rejected as indefinite in the previous Office Action.

In view of Applicants canceling the rejected claims, and presentation of new claims 102-131, the rejection is considered moot.

Rejection under 35 USC § 112, first paragraph (written description)

Claims 21, 23, 25-27, 84 and 86-95 have been rejected as lacking adequate written description in the previous Office Action.

However, in view of the presentation of new claims following the new restriction requirement, the rejection is withdrawn.

Rejection under 35 USC § 112, first paragraph (enablement)

Claims 21, 23, 25-27 and 83-95 have been rejected as not being enabled in the previous Office Action.

However, in view of the presentation of new claims following the new restriction requirement, the rejection is withdrawn.

Rejection under 35 USC § 102(b) – Sano et al.

Claims 21, 23, 25-27, 83-85 and 89 have been rejected as anticipated by Sano *et al* in the previous Office Action.

However, Applicants' arguments have been found persuasive and the rejection is withdrawn.

Rejection under 35 USC § 102(b) – Sermjian et al., Van Camp et al., Lowell et al, or Sellar et al.

Claims 21, 23, 25-27, 83-85 and 89 have been rejected as anticipated by Sermjian *et al.*, Van Camp *et al.*, Lowell *et al*, or Sellar *et al.* in the previous Office Action.

However, Applicants' arguments have been found persuasive and the rejection is withdrawn.

New Grounds of Rejection

Objection to Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. See MPEP § 606.01. The following title is suggested: "Assay Methods Using Peptides Having a β-Secretase Cleavage Site."

Claim Objections

Claim 130 is objected to for the typographical error "t transgenic." Correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 102-131 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regards as the invention.

Claim 102, and all claims that depend therefrom, are indefinite for reciting the phrase "*wherein a human aspartyl protease encoded by the nucleic acid sequence of SEQ ID NO:1 or SEQ ID NO:3 (Hu-Asp2) cleaves said peptide between P1 and P1'*," because it is not clear how this limitation further affects the method. For example, claim 102 is a "method" claim, but the quoted limitation is not clearly conveyed as a positive, proactive method step. If Applicants are intending to define the P_2P_1-$P_1'P_2'$ by a physicochemical property, function and/or an activity, Applicants should claim the property/activity more clearly (*e.g.*, "wherein P_2P_1-$P_1'P_2'$ has [a certain] Hu-Asp2 activity"). Correction is required.

Claim 102, and all claims that depend therefrom, are indefinite for reciting the phrase "does not comprise the *corresponding P_2P_1-$P_1'P_2'$ portion* of amino acid sequence *depicted in SEQ ID NO*: 19, ..." because it is not clear what sequences fall within the scope of the claims. The SEQ ID Nos themselves do not "depict" the corresponding P_2P_1-$P_1'P_2'$ portion of the amino acid. Table 1, however, appears to depict the corresponding 4-mer amino acid sequences that Applicants wish to exclude from the substrate polypeptide, wherein the hyphen represents the scissile bond between P_1 and P_1', such as substrates comprising the amino acid sequences NL-DA, KM-DA, N(Nle)-DA, or any of the others listed in the table as identified by SEQ ID NO.

Claim 131 is indefinite because the limitations of the "protease" in claim 131 broaden the scope of the claim (*i.e.*, the sequence limitations are narrower in claim 102). Accordingly, the claim is considered indefinite since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. See MPEP § 2173.05(c).

Claim Rejections - 35 USC § 112, first paragraph (written description)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 102-109 and 117-131 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As Applicants correctly point out in their previous Reply, the written description requirement is distinct from the enablement requirement; this was first pointed out by the court in *In re Ruschig*, 379 F.2d 990, 154 USPQ 118 (CCPA 1967), and clarified in *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). The issue of whether the claimed subject matter is adequately supported/described by the specification, is a question of *fact*. *Id.* at 1563, 19 USPQ2d at 1116.

When considering whether the claimed subject matter complies with the written description requirement, Applicants' disclosure should be read in light of the knowledge possessed by those skilled in the art.

> "[T]he disclosure in question must be read in light of the knowledge possessed by those skilled in the art, and that knowledge can be established by affidavits of fact composed by an expert, and by referencing to patents and publications available to the public..."

In re Lange, 644 F.2d 856, 863, 209 USPQ 288, 294. *See also, In re Alton*, 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).

Applicants enjoy the presumption that their patent application is valid and all statements contained therein are accurate; it is the PTO's burden to demonstrate why any of Applicants claims should be rejected or why any of Applicant's statements should be doubted.

> "it is incumbent upon the Patent Office, whenever a rejection... is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure."

In re Marzocchi, 439 F.2d 220, 224, 169 USPQ 367, 370. If successful in presenting such evidence and argument, the burden then shifts to the Applicant to provide evidence that would convince one to the contrary.

The Invention in General

A component of Applicants' invention is directed to a method for screening inhibitors of an enzyme (class of enzyme) involved in the progression of Alzheimer's disease (AD). Applicants provide a clear and succinct background of the invention by detailing certain biochemical pathways in the formation of the plaques responsible for AD. An origin of these plaques is the amyloid protein precursor (APP), which when first processed by an enzyme having β-secretase activity, followed by an enzyme having γ-secretase activity, causes the formation of a 40/42 amino acid peptide plaque know as Aβ.

Accordingly, the development of methods for identifying compounds that might one day serve as potential β-secretase inhibitors are undoubtedly needed by the biomedical community in order to accelerate the development of AD drug candidates. As Applicants suggest, such a demand would benefit from the identification of a substrate that is more sensitive to the activity of β-secretase for use in an assay in identifying and characterizing potential inhibitors/drug candidates.

The Claimed Invention

The claimed invention (*e.g.*, claim 102) is broadly directed to a method for assaying for a modulator of β-secretase activity comprising contacting: (i) a peptide having β-secretase activity, with (ii) a peptide/substrate of the generic formula P_2P_1-$P_1'P_2'$, wherein the amino acid "P" values are defined, but excluding certain peptides identified by SEQ ID NO, and measuring the activity in the presence and absence of a potential inhibitor compound.

Certain narrower embodiments of the claimed invention are presented in various dependent claims. Some of these claims further limit the various values for certain amino acid positions in the substrate sequence; other claims limit certain other aspects, including but not limited to the claimed labels, the length of the substrate, the presence of a quenching moiety, the polypeptide with the β-secretase activity, and assay milieu.

The Supporting Disclosure

Applicants' supporting disclosure contains numerous embodiments of the invention. Pages 3 through 5 list a number of different chemical genera of a peptide fragment comprising various groups of amino acids that have a scissile bond when reacted with a protein having β-secretase activity. For example, on page 3, the peptide fragment is defined by the genus P_2P_1-$P_1'P_2'$, wherein P_2 is defined as a charged amino acid, a polar amino acid or an aliphatic amino acid but is not an aromatic amino acid, P_1 is an aromatic amino acid or an aliphatic amino acid but not a polar amino acid or a charged amino acid; P_1' is a charged amino acid, or aliphatic amino acid, or a polar amino acid but is not an aromatic amino acid; and P_2' is an uncharged aliphatic polar amino acid or an aromatic amino acid but not a charged amino acid; wherein the peptide is cleaved between P_1 and P_1' by two certain human aspartyl proteases, and has certain other provisos.

Certain other embodiments further limit an aspect of the invention by describing the peptide fragments as certain sequence encoded by $P_4P_3P_2P_1$-$P_1'P_2'P_3'$, and list the possible amino acids that could by used at the corresponding P values. Applicants provide some guidance with respect to the preferred P values, and list those values on page 5. On page 6, Applicants describe particular sequences that are preferred peptides of the present invention by SEQ ID NO.

The disclosure describes a number of substrates encompassed by the claimed chemical genus that produce β-secretase activity, and conveniently groups these substrates by sequence similarity to illustrate certain trends or correlations (Tables 2-5, and description thereof). Following Table 3 on pages 21-23, the disclosure describes the particular substitutions and the resulting effects on activity (objective statements; not an explanation of the physicochemical properties as it relates to the enzyme system). The discussion following Table 5 on pages 25 and 26 is similar. The disclosure does, however, indicate on page 26 that extension of the N-terminal region of a particular peptide fragment is expected to enhance activity.

On pages 28 and 29, the disclosure describes the amino acids by their well-known characteristics and explains hydropathic indexing. In particular, the specification states:

> "It is accepted that the relative hydropathic character of the amino acid contributes to the secondary structure of a resultant protein or peptide, which in turn defines the interaction of that protein with other molecules, for example, enzymes, substrates, receptors, DNA, antibodies, antigens,

> and the like. Each amino acid has been assigned a hydropathic index on the basis of their hydrophobicity and charge characteristics (Kyte & Doolittle, *J. Mol. Biol.*, 157(1):105-132, 1982, incorporated herein by reference). Generally, amino acids may be substituted by other amino acids that have a similar hydropathic index or score and still result in a protein with similar biological activity *i.e.*, still obtain a biological functionally equivalent protein or peptide. In the context of the peptides of the present invention, a biologically functionally equivalent protein or peptide will be one which is still cleaved by β-secretase at a rate exceeding the rate of cleavage of a nature [*sic*] APP peptide comprising SEQ ID NO: 20."

Applicants' disclosure, page 29, lines 6-18.

Table 6 lists Applicants exemplary amino acids that they consider to be useful at the positions P_4, P_3, P_2, P_1, P_1', P_2', P_3' and P_4'. It appears that the selection of these amino acids is based, in-part, on certain working examples (*i.e.*, tested peptide fragments having β-secretase activity), amino acids that are listed as equivalents to the working examples based on the hydropathic index, and possibly certain prophetic examples as listed on pages 30 and 31. It further appears that the combination of individual amino acids at each of the P values that form the claimed P_2P_1-P_1'P_2' peptide fragment are independently selected.

Additionally, the description discloses a number of other embodiments relevant to Applicants' invention, such as labels, fusion proteins, detection schemes, transgenic animals, certain laboratory preparation techniques, etc.

Regents of Cal. v. Lilly, and Enzo Biochem v. Gen-Probe

Two cases that deal with the written description requirement and that are related to the general technological arts of the claimed invention are *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997), hereinafter "*Lilly*," and *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 956, 63 USPQ2d 1609 (Fed. Cir. 2002), hereinafter "*Enzo II*," which was reheard by the Federal Circuit following the original holding in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 285 F.3d 1013, 62 USPQ2d 1289 (Fed. Cir. 2002), hereinafter "*Enzo I.*"

In 1977, the Regents of the University of California ("UC") successfully cloned the rat insulin gene and filed a series of patent application, and obtained broad claims directed not only

to a plasmid containing the inserted cDNA encoding the rat insulin protein, but also plasmids containing an inserted cDNA encoding the insulin protein of a vertebrate, a mammal, and a human. Eli Lilly argued that the asserted claims in the UC patents were invalid for failure to provide an adequate written description of the subject matter of the asserted claims. The district court ruled in favor of Eli Lilly with regard to lack of written description of UC's patents ("the '525 patent" and "the '740 patent"), and UC appealed. Among others, claims 1 of the '525 patent, and claim 5 of the '740 patent, were found to lack adequate written description. Claim 1 of the '525 patent reads as follows: "A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin." Claim 5 of the '740 patent reads: "A DNA transfer vector comprising a deoxynucleotide sequence coding for human proinsulin consisting essentially of a plus strand having the sequence: [nucleotides that encode human proinsulin, described in structural terms]."

On appeal, the Federal Circuit first considered the holding that claim 5 was invalid for lack of written description. *Lilly*, 43 USPQ2d at 1404. The court stated:

> "Claim 5 is directed to a recombinant procaryotic microorganism modified so that it contains "a nucleotide sequence having the structure of the reverse transcript of an mRNA of a [human], which mRNA encodes insulin." Thus, the definition of the claimed microorganism is one that requires [page 1405] human insulin-encoding cDNA. The patent describes a method of obtaining this cDNA by means of a constructive example, Example 6. This example, however, provides only a general method for obtaining the human cDNA (it incorporates by reference the method used to obtain the rat cDNA) along with the amino acid sequences of human insulin A and B chains. Whether or not it provides an enabling disclosure, it does not provide a written description of the cDNA encoding human insulin, which is necessary to provide a written description of the subject matter of claim 5. The name cDNA is not itself a written description of that DNA; it conveys no distinguishing information concerning its identity. While the example provides a process for obtaining human insulin-encoding cDNA, there is no further information in the patent pertaining to that cDNA's relevant structural or physical characteristics; in other words, it thus does not describe human insulin cDNA. Describing a method of preparing a cDNA or even describing the protein that the cDNA encodes, as the example does, does not necessarily describe the cDNA itself. No sequence information indicating which nucleotides constitute human cDNA appears in the patent, as appears for rat cDNA in Example 5

> of the patent. Accordingly, the specification does not provide a written description of the invention of claim 5."

Id., 43 USPQ2d at 1404, 1405. In quoting *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572 (Fed. Cir. 1997)), the court stated that in order to comply with the written description requirement, and inventor must "'describe[e] the invention, with all its claimed limitations, not that which makes it obvious,' and [use] 'such descriptive means as words, structures, figures, diagrams, formulas, etc:, that set forth the claimed invention.'" *Id.* 43 USPQ2d at 1404, (quoting Lockwood, 107 F.3d at 1572).

It was further explained that a disclosure of a single species (in this case rat insulin) does not describe the broad classes of vertebrate or mammalian insulin cDNAs. A generic statement of _____ insulin cDNA "without more . . . does not distinguish the claimed genus from others, except by function." *Id.*, 43 USPQ2d at 1406. Unlike chemical formulae, which indicate specifically what is encompassed in the generic claims, _____ insulin cDNA "does not define any structural features commonly possessed by members of the genus that distinguish them from others," and is not an adequate written description. *Id.*, 43 USPQ2d at 1406.

The Federal Circuit revisited the written description requirement in *Enzo I and II*[1]. Enzo Biochem ("Enzo") held a patent to nucleic acid probes that selectively hybridize to the genetic material of the bacteria that cause gonorrhea. Enzo made three hybridization probes that selectively hybridized to six publicly deposited strains of *N. gonorrhoeae* over six publicly deposited strains of *N. meningitides* at a ratio of greater than 50 to 1. *Enzo I,* at 1016. Enzo sued Gen-Probe for infringement. The district court held that the claims in Enzo's patent "were invalid for failure to meet the written description requirement" because the claimed invention was defined only by its biological function, the ability to hybridize to *N. gonorrhoeae*. The district court also rejected Enzo's argument that the deposit of the probes at American Type Culture Collection "inherently disclosed that the inventors were in possession of the claimed sequences" because the depositing of samples concerned only enablement.

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[1] Since *Enzo II*, the district court on remand invalidated certain claims in the relevant patents under the "on-sale" bar, however, on further appeal, the Federal Circuit has held that it lacked jurisdiction when an unadjudicated counter-claim was pending in the case, as asserted by Gen-Probe. *Enzo Biochem, Inc. v. Gen-Probe, Inc.* case no. 04-1570 (Fed. Cir. 2005).

On appeal, a split panel affirmed the district court's ruling in *Enzo I.* The panel concluded that the ability of the broadly claimed probes to hybridize specifically to *N. gonorrhoeae* may reasonably describe the probe's function, but not the probe itself, and is not a distinctive "chemical property" of the claimed sequences. However, the dissent argued that "by describing the degree of hybridization of the claimed nucleotide sequences, the specification may adequately describe the structure of the claimed sequences [to a PHOSITA]." *Id.*, at 1026. First, the hybridization of the probes to "known DNAs is a direct result of the structure of the nucleotide sequence." Second, the probe's targets were not novel, and the specification indicated "that the structure of the targets [was] at least somewhat known to [a PHOSITA]." Therefore, the dissent felt that the claimed probes might be described by their ability to selectively hybridize to *N. gonorrhoeae*.

The panel also held that the narrow claims to the deposited probes were not properly described. Although the deposit showed possession, "[a] showing of 'possession' is secondary to the statutory mandate 'that [t]he specification shall contain a written description . . .' and that requirement is not met if . . . the specification does not adequately describe the claimed invention" despite a showing of possession. *Id.* at 1021. The court referred to a previous holding that "'[a]n accession number and deposit date add nothing to the written description of the invention" and "'a deposit is not a substitute for a written description of the claimed invention.'" Conversely, the dissent argued that "a specification that describes the invention by reference to a deposit of a sample of the invention in a recognized depository is an ideal way of satisfying the written description requirement." *Id.* at 1027. The dissent reasoned that the main purpose of the written description requirement was "to provide notice to competitors and the public of the scope of the patent claims," and since the public deposit of the probes "provides a precise and unmistakably clear description of the invention that is accessible to the public," the competitors and the public would clearly determine the scope of the patent claims by obtaining a sample of the probes from the public depository. *Id.*

Last, the panel majority rejected Enzo's assertion that reduction to practice satisfies the written description requirement because "[a]lthough an actual reduction to practice . . . may demonstrate possession of an embodiment of an invention, it does not necessarily describe what the claimed invention is...," and stated that "Enzo has merely disclosed that it obtained the

sequences, but it has not identified them." *Id.* at 1023. Subsequently, the panel granted rehearing and reversed its decision that a deposit does not satisfy the written description requirement.

On rehearing in *Enzo II*, the panel decided that "[not] all functional descriptions of genetic material fail to meet the written description requirement." *Enzo II*, at 1324. The panel adopted the PTO's guidelines governing the written description requirement, and stated that "functional characteristics when coupled with a known or disclosed correlation between function and structure" can meet the requirements of the written description. *Id.* at 1324-25. The panel then addressed whether the deposits of the claimed probes could constitute an adequate description of their sequences and whether the description requirement is met for all of the claims on the basis of the functional ability of the probes to hybridize to strains of *N. gonorrhoeae* that are publicly accessible by deposit.

Enzo argued that its deposits of the claimed probes were an adequate description of their sequences. The court held that the written description requirement can be met by "reference in the specification to a deposit in a public depository, which makes its contents accessible to the public when it is not otherwise available in written form..." *Id.* at 1325. The probes that were actually deposited, therefore, were adequately described in the specification. *Id.* at 1326. However, the panel did not determine whether the deposited probes served as an adequate written description for the broader claims directed to discrete, mutated nucleotide sequences selected from any of the three deposited probes and remanded this issue to the district court. *Id.* at 1326-27. The panel also decided that the issue of whether the three deposited sequences were representative of the broader genus claims to any sequence hybridizing in the manner described was one that should be decided upon remand to the district court. *Id.* at 1328.

The panel then turned to whether "the disclosed correlation of the function of hybridization with the bacterial DNA" adequately described all of Enzo's claims. *Id.* at 1328. Enzo argued that "[t]he description and claiming of biological materials by their affinity to other materials that are clearly identified in the specification and claims (the particular deposited strains of *N. gonorrhoeaeand N. meningitidis*) inherently specifies structure, and is routine in this field" *Id.* The court replied:

> "Again, as with the claimed nucleotide sequences, the sequences of the genomic DNA of those bacteria are not disclosed, perhaps because such sequencing would have been unduly burdensome at the time of Enzo's invention. '659 patent, col. 3, ll. 40-46 (noting that it would take 3,000 scientists one month to sequence the genome of one strain of *N. gonorrhoeae* and one strain of *N. meningitidis*). However, as those bacteria were deposited, their bacterial genome is accessible and, under our holding today, they are adequately described in the specification by their accession numbers. *Because the claimed nucleotide sequences preferentially bind to the genomic DNA of the deposited strains of N. gonorrhoeae and have a complementary structural relationship with that DNA, those sequences, under the PTO Guidelines, may also be adequately described.* Although the patent specification lacks description of the location along the bacterial DNA to which the claimed sequences bind, Enzo has at least raised a genuine issue of material fact as to whether a reasonable fact-finder could conclude that the claimed sequences are described by their ability to hybridize to structures that, while not explicitly sequenced, are accessible to the public. *Such hybridization to disclosed organisms may meet the PTO's Guidelines stating that functional claiming is permissible when the claimed material hybridizes to a disclosed substrate. That is a fact question.* We therefore conclude that the district court erred in granting summary judgment that the claims are invalid for failure to meet the written description requirement. On remand, *the court should consider whether one of skill in the art would find the generically claimed sequences described on the basis of Enzo's disclosure of the hybridization function and an accessible structure*, consistent with the PTO Guidelines. If so, the written description requirement would be met."

Id. at 1328 (emphasis added).

Finally, the panel addressed whether "the written description requirement for the generic claims [was] necessarily met . . . because the claim language appears *in ipsis verbis* in the specification." *Id.* The panel stated:

> "Even if a claim is supported by the specification, the language of the specification, to the extent possible, must describe the claimed invention so that one skilled in the art can recognize what is claimed. The appearance of mere indistinct words in a specification or a claim, even an original claim, does not necessarily satisfy that requirement. One may consider examples from the chemical arts. A description of an anti-inflammatory steroid, *i.e.*, a steroid (a generic structural term) described even in terms of its function of lessening inflammation of tissues fails to distinguish any steroid from others having the same activity or function.

> Similarly, the expression "an antibiotic penicillin" fails to distinguish a particular penicillin molecule from others possessing the same activity. A description of what a material does, rather than of what it is, usually does not suffice. *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. The disclosure must allow one skilled in the art to visualize or recognize the identity of the subject matter purportedly described."

Id. at 1328. However, the panel stated that showing possession of the invention by the date of filing of the application is "merely . . . a purpose of the written description requirement" and that "[a]pplication of the written description requirement . . . is not subsumed by the 'possession' inquiry." *Id.* at 1328-29. The court concluded that a showing of possession of the invention or a reduction to practice "does not cure the lack of a written description in the specification, as required by statute." *Id.* at 1330.

Therefore, the court's ruling on rehearing found that possession of the invention at the time of filing is a purpose of the written description requirement, not the test for adequacy of the written description. Instead, the written description requirement must convey to a PHOSITA what is claimed as the invention. In other words, the purpose of patent claims is to draw the boundaries of the claimed invention, and it is the written description that clearly illustrates what aspects of the invention is within those boundaries. In order to satisfactorily describe a genus, the written description must set forth the "common features possessed by members of the genus that distinguished them from others... [and] describe a sufficient number of species within the very broad genus to indicate that the inventors had made a generic invention, *i.e.*, that they had possession of the breadth of the genus, as opposed to merely one or two such species" *Id.* at 1327.

The State of the Art

A number of reference are relied upon as factual support in challenging certain statements made in the instant application and as a basis for rejecting the claims for lacking written description. For example, Gruninger-Leitch *et al.* ("Leitch"), *J. Biol. Chem. 277(7)*:4687-4693 (**2002**); Majer *et al.* ("Majer"), *Protein Science 6*:1458-1466 (**1997**); Sauder *et al.* ("Sauder"), *J. Mol. Biol. 300*:241-248 (**2000**); Shi *et al.* ("Shi"), *J. Alzheimer's Disease 7*:139-148 (**2005**); and Tomasselli *et al.* ("Tomasselli"), *J. Neurochemistry 84*:1006-1017 (**2003**);

taken together, suggest that Applicants were not in possession of the claimed invention at the date of filing, and further, have not provided such sufficient description to support the invention as is broadly claimed. Specifically, the art as a whole provides sufficient evidence that demonstrates that Applicants' particular P_2P_1-$P_1'P_2'$ species, taken in combination with their supporting disclosure, does not support the breadth of the claimed P_2P_1-$P_1'P_2'$ genus.

Leitch discloses a comparison study between certain proteases including BACE, BACE2, cathepsin D and E, napsin A, pepsin and rennin, and teaches that BACE presents itself as an ideal target for AD treatment. In particular, Leitch teaches the specificity and activity of a number substrates that are cleavable by BACE in comparison to other proteases. Certain factors identified in Leitch's teachings would suggest that Applicants' claimed genus is unsupported by their disclosure include the following factors: i) the effects of, and importance, of amino acids further from the scissile bond of the substrate, such as P_4, P_3, P_3' and P_4'; ii) the length of the substrate required for cleavage by the BACE enzyme; and iii) certain *in vitro* and *in vivo* differences in activity, wherein any single factor may or may not be coupled to any other factor(s). Table 1 illustrates the effects of certain substrate mutations compared to the Swedish type APP substrate. A single amino acid mutation at P1' of the Swedish mutant APP β-cleavage site (NL-D → NL-A), results in an 84% drop in activity. Even more surprisingly, the P4K substrate which differs from the Swedish mutant APP β-cleavage site (NL-D) by a single amino acid at P_4, yet retains the same P_2P_1-$P_1'P_2'$ sequence, results in a 50-fold drop in activity (Table 1 on page 4689). These mutations and effects are relevant to the breadth and subject matter of Applicants' claims, and do not appear to be remedied by the art or Applicants' disclosure.

Similar to Applicants' approach (see pages 20-30 of the instant application), Leitch progressively optimizes certain substrates based on observed preferences in BACE substrates (pages 4690-4691). Although Applicants have optimized their sequences based on insulin and ubiquitin, such studies and a general reference to the hydropathic indexing of substrates does little to provide a structure-activity nexus for linking the broad array of species to the relatively large claimed genus. Leitch demonstrates a number of amino acids substitutions for certain positions within the cleavable peptide substrate, and reveals that certain amino acid combinations

appear to be interdependent.[2] Leitch also teaches that the *in vivo* and *in vitro* differences can affect activities, possibly due to an orientation effect and the cell lumen (page 4692), and can be further complicated by the size of the substrate (page 4693).

Given the fact that the amino acid substitution effects are not necessarily additive, and that drastic effects in activity can be observed by changing amino acids either in the P_2P_1-$P_1'P_2'$ region, support for Applicants' genus is reasonably challenged by the teaching of Leitch. As a result of each of these factors, considered independently or as having a cumulative effect on the substrate/enzyme relationship, one of ordinary skill in the art would doubt that Applicants had adequately described the invention as broadly claimed.

Tomasselli also reports experimental findings that demonstrate that the claimed genus is not supported by the disclosed species because of amino acid interdependence and *in vitro* and *in vivo* differences in activity:

> "Enzyme subsites are interdependent and occupancy of a subsite by two 'well tolerated', but different amino acids, may differentially influence the amino acid preferences at the other subsites."

Tomasselli at page 1014, column 1; and again regarding the interdependence of amino acids:

> "Our findings indicate that amino acid preference at a specific site has to be regarded in the context of the peptide sequence rather than of maximal statistical occurrence of that amino acid at that specific position in the substrate. *A P1 Leu may be highly preferred in a library of peptide substrates, but Tyr is optimal at this position in our best substrate because of its interdependence upon its neighboring P-site substituents.* We have produced an optimal BACE1 substrate by systematic changes in individual P-sites considered globally with respect to the overall sequence, and by N-terminal extension of the peptides with the naturally occurring APP sequence."

Id. at page 1014, column 2 (emphasis added). Regarding Tomasselli's "systematic" approach, however, neither Applicants nor Tomasselli provide sufficient description to link all of the claimed species to the genus. Instead, one of ordinary skill in the art would consider the approaches of Leitch and Turner to be "systematically" different, but still systematic. For example, Shi discloses a BACE substrate identified by a library approach that is about 3-4 fold

[2] Leitch teaches that "the hydroxylamino acids Thr and Ser were found at position P2 only in combination with Ser

scissile than that disclosed by Tomasselli (Shi at page 141, column 2). Although certain approaches may be better served for identifying a few particular species, Applicants' and Tomasselli's approaches do not sufficiently describe the breadth of the genus as claimed.

Majer discloses a series of compounds produced through a systematic approach for optimizing inhibitor polypeptides to cathepsin D, an aspartic protease. Similar to optimizing BACE substrates with a scissile bond, a number of factors are important in substrate/inhibitor optimization, including but not limited to, hydropathy, orientation of the amino acid side chains, backbone configuration, hydrogen bonding, side chain length, and a number of subsite considerations, such as steric interactions, solvation, etc. Majer also teaches that there are additional important considerations besides the P_2P_1-$P_1'P_2'$ amino acid residues (pages 1458-1465), and that amino acid substitutions are not necessarily additive (page 1462).

Many of the claimed amino acid substitutions do not necessarily follow from any disclosure, or the corresponding systematic approaches. One sequence that only differs from Applicants' most active substrate (SY-EV) is the sequence GY-EV as disclosed in Sauder (see Figure 4 on page 246, and description thereof on page 245), however, this sequence has drastically reduced in activity in comparison. Based on the hydropathic index, the single value difference between S → G is –0.4 (see page 110 of Kyte and Doolittle, *J. Mol. Biol. 157(1)*:105-132 (**1982**)). Vassar discloses that a substitution of a single amino acid to P1 of the APPwt (M → V), results in elimination of the scissile bond. Although the difference in going from M → V has a single position value difference in the hydropathic index of 2.3, the wt to Sweedish mutation has a hydropathic difference of comparable magnitude at 2.0 at P1 (Kyte at page 110).

P_2P_1-$P_1'P_2'$ Sequence	***Description***
KM-DA	APPwt
NL-DA	Swedish mutant with high increase in activity
KV-DA	lacks activity
GY-EV	low activity; the wt β'-secretase site
SY-EV	Applicants' most active sequence fragment
NF-EV	Shi's most active sequence fragment

However, it is not truly clear from Applicants' or any other "systematic" approach, or the teachings in the art, what effects certain amino acid substitutions will have on a substrate, even if

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at P1'."

the substitution is sometimes preferred for one particular substrate, or by relying on hydropathic indexing.

Accordingly, for at least these reasons, Applicants have not adequately described the invention for the breadth that is claimed. It thus appears that Applicants were not in possession of the claimed invention at the time the application was filed, the structure-function relationship between the protease and the scissile substrates have not been adequately set forth, and that Applicants' species do not support the claimed genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 102-115, 117-121 and 123-131 are rejected under 35 U.S.C. 102(e) as being anticipated by Fang *et al.* ("Fang"), U.S. Patent Appl Pub. No. 2003/0096864 A1, filed on June 29, 2001, which claims the benefit of U.S. Provisional Application 60/215,323, filed on June 30, 2000.

Claim 102 is directed to a method for assaying for a modulator of β-secretase activity comprising contacting: (i) a peptide having β-secretase activity, with (ii) a peptide/substrate of the generic formula P_2P_1-$P_1'P_2'$, wherein the amino acid "P" values are defined, but excluding certain peptides identified by SEQ ID NO, and measuring the activity in the presence and absence of a potential inhibitor compound. Certain claims further limit the substrate sequence to P_2P_1-$P_1'P_2'$ = SY-EV, as in claim 110, and certain other claims limit the substrate to polypeptide sequences comprising the sequence GLTNIKTEEISEISY-EVFRWKK (SEQ ID NO: 191), as in claim 113.

Fang teaches assays for screening purportedly novel AD inhibitors using synthetic APP substrates. Fang teaches that synthetic APP substrates that can be cleaved by β-secretase and

having N-terminal biotin and made fluorescent by the covalent attachment of oregon green at the Cys residue is used to assay β-secretase activity in the presence or absence of the inhibitory compounds of the invention. One of the useful substrates taught by Fang for such assays includes the polypeptide sequence as followed:

Biotin-GLNIKTEEISEISY-EVEFRC[oregon green]KK (SEQ ID NO: 3).

Fang details certain of the assay procedures, and teaches that the assays are carried out in the presence and absence of the putative inhibitor (paras. 1137 to 1161); Fang also sites a number of art-related references that teach the contemplated assay methods (para. 1138). The oregon green moiety constitutes a first label, the biotin constitutes a second label, and the substrate has a rate of cleavage faster than the Swedish mutant APP (inherent property; same sequence as Applicants' sequence). Accordingly, each of claims 102-115, 117-121 123 are anticipated. Fang teaches using the enzyme as taught by Sinha[3] (para. 1138), which is the same as Applicants' enzyme in SEQ ID NO: 2, and may be extracted from natural sources or transfected cells; accordingly, claims 126-128 are anticipated. Fang teaches the cellular assay of claim 129 (paras. 1162-1164). Fang teaches the transgenic animal assay of claim 130 (paras. 1165-1169). The nucleic acid sequence in Sinha as referenced by Fang is the same as Applicants' SEQ ID NO: 1 (claim 131). Accordingly, claim 131 is anticipated by Fang.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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[3] Sinha *et al.*, *Nature 402*:537-540 (1999) – the 501 a.a. β-secretase, and the p501 cDNA on page 539. Since Sinha is incorporated by reference (Fang, paras. 1138 and 1057), in particular the teachings as it pertains to the sequence identity of the β-secretase, Fang is treated as teaching these limitations. *See, Advanced Display Systems Inc. v. Kent State University*, 54 USPQ2d 1673 at 1679 (Fed. Cir. 2000) – "Incorporation by reference provides a method for integrating material from various documents into a host document --a patent or printed publication in an anticipation determination-- by citing such material in a manner that makes clear that the material is effectively part of the host document as if it were explicitly contained therein. *See General Elec. Co. v. Brenner*, 407 F.2d 1258, 1261-62, 159 USPQ 335, 337 (D.C. Cir. 1968); *In re Lund*, 376 F.2d 982, 989, 153 USPQ 625, 631 (CCPA 1967). To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. *See In re Seversky*, 474 F.2d 671, 674, 177 USPQ 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which [page 1680] is incorporated and where it is to be found"); *In re Saunders*, 444 F.2d 599, 602-03, 170 USPQ 213, 216-17 (CCPA 1971) (reasoning that a rejection for anticipation is appropriate only if one reference "expressly incorporates a particular part" of another reference.

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 102-115 and 117-131 rejected under 35 U.S.C. 103(a) as being unpatentable over Fang and Zhang et al. ("Zhang"), U.S. Patent No. 6,248,904, issued on June 19, 2001.

The scope of claims 102-115, 117-121 and 123-131, and the corresponding limitations taught by Fang have been set forth above in the rejections under 35 USC § 102(e), and are herein incorporated by reference.

Fang does not teach a fluorogenic substrate having a detectable label and a quenching moiety for assay purposes.

Zhang teaches certain novel fluorescent dyes, novel fluorogenic and fluorescent reporter molecules and new enzyme assay processes that can be used to detect the activity of certain proteases in whole cells, cell lines and tissue samples derived from any living organism or organ. The reporter molecules and assay processes can be used in drug screening procedures to identify compounds which act as inhibitors or inducers of the proteases in whole cells or tissues. Zhang's invention also relates to novel fluorogenic peptide substrates and fluorescent reporter molecules and new enzyme assay processes that can be used to detect their protease activity. The fluorogenic substrates taught in Zhang have a fluorescent reporter and a quencher (*i.e.*, intramolecular quenching or energy transfer accepter moiety; see *Detailed Description of the Invention*, especially col. 20, line 32 through col. 21, line 37).

One of ordinary skill in the art would have been motivated to incorporate the fluorophore-quencher strategy or the FRET pair strategy of Zhang with the secretase inhibitor substrate assay of Fang because of the advantages that FRET/quenching measurements have over polarization measurements of Fang (*i.e.*, the elimination of more complicated polarization requirements when performed in whole cell assays). FRET and quenching assays allow one to more simply follow the fluorescence intensity at a given wavelength. One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the claimed invention because each of Fang and Zhang teach protease inhibitor assays using fluorogenic substrates

(i.e., substituting Fang's biotin with Zhang's donor/acceptor/quencher moiety). Accordingly, the invention as a whole was *prima facie* obvious at the time it was invented.

Conclusions

No claim is allowable.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to J.S. Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached on 8:30 AM to 5:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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